

# ATP Citrate Lyase (ACL) catalyzes the production of cytosolic acetyl CoA

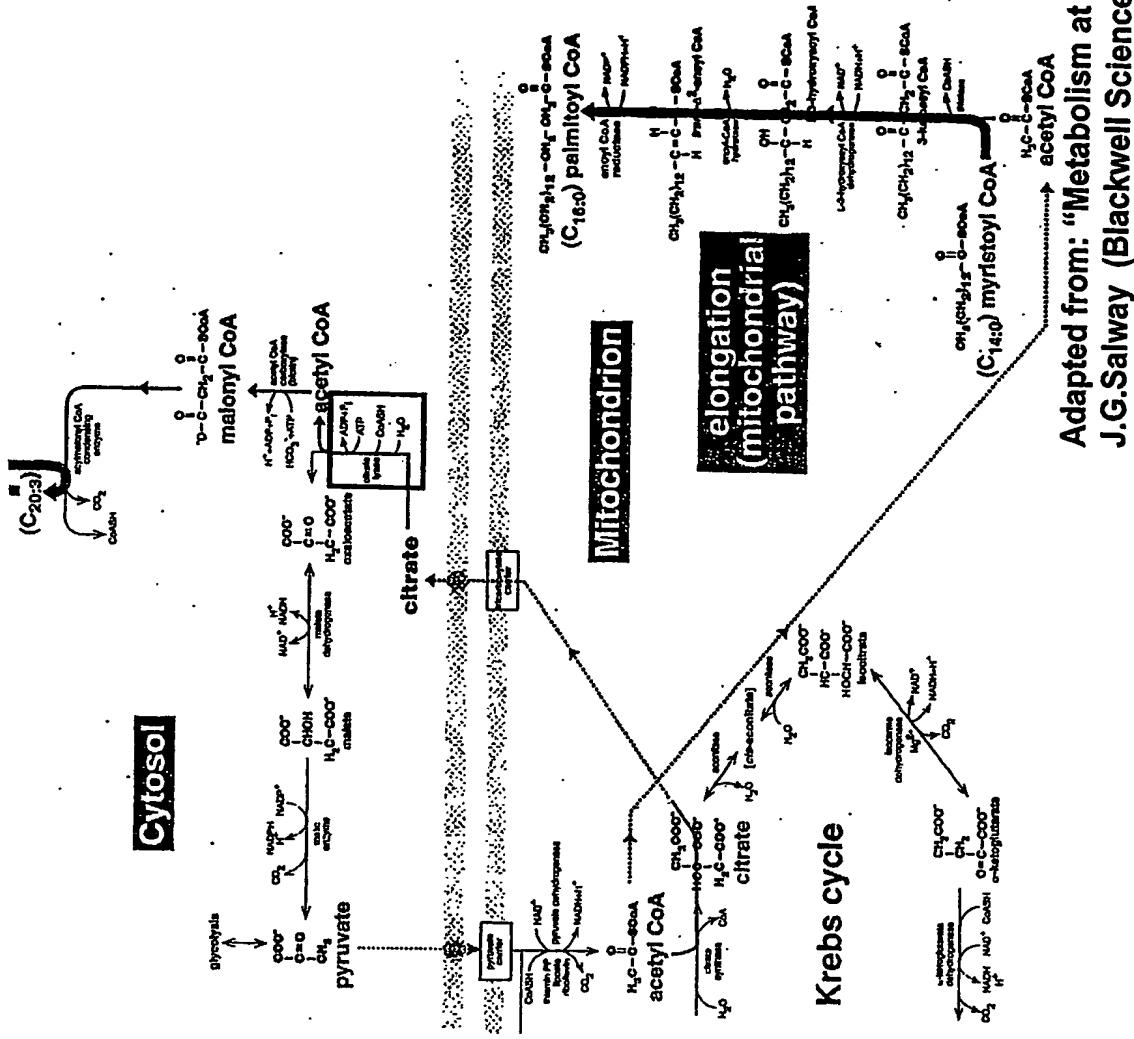


Figure 1

Adapted from: "Metabolism at a glance" (1999)  
J.G.Salway (Blackwell Science Ltd, England)

**ACL activity is downregulated in quiescent cells via  
a post-transcriptional mechanism**

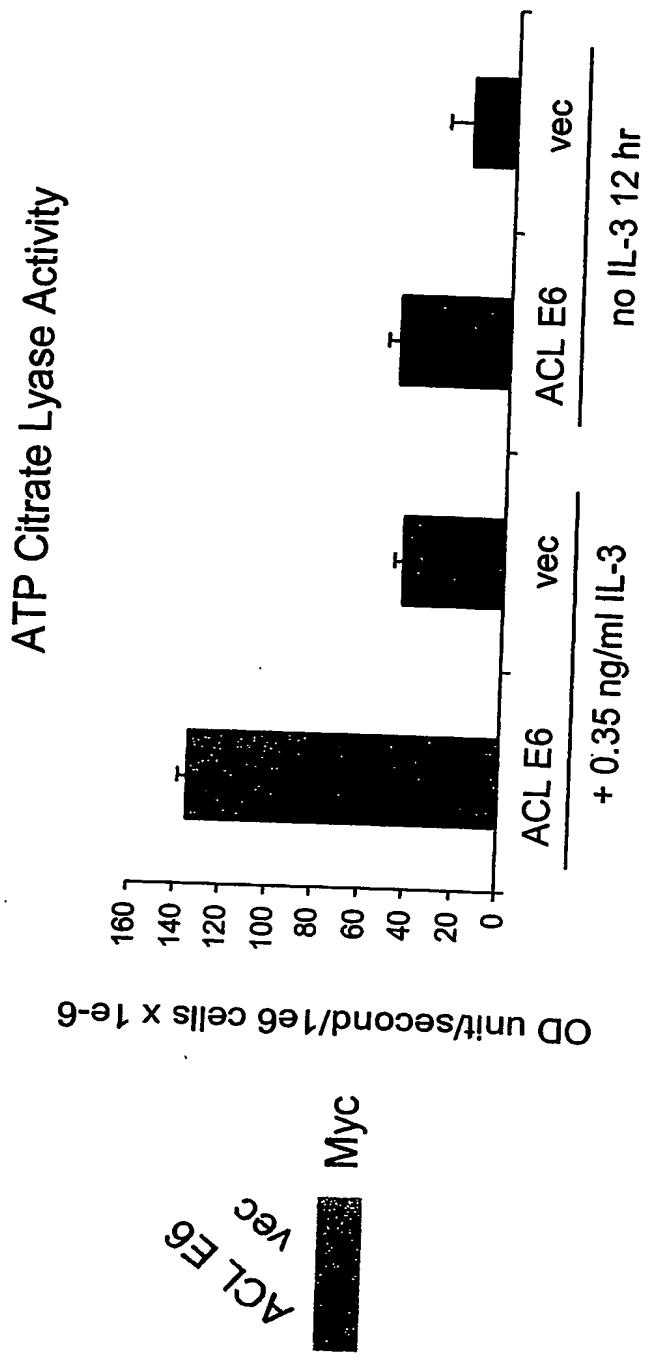


Figure 2

**(-)-Hydroxycitrate inhibits cell survival in a dose-dependent fashion at millimolar concentrations**

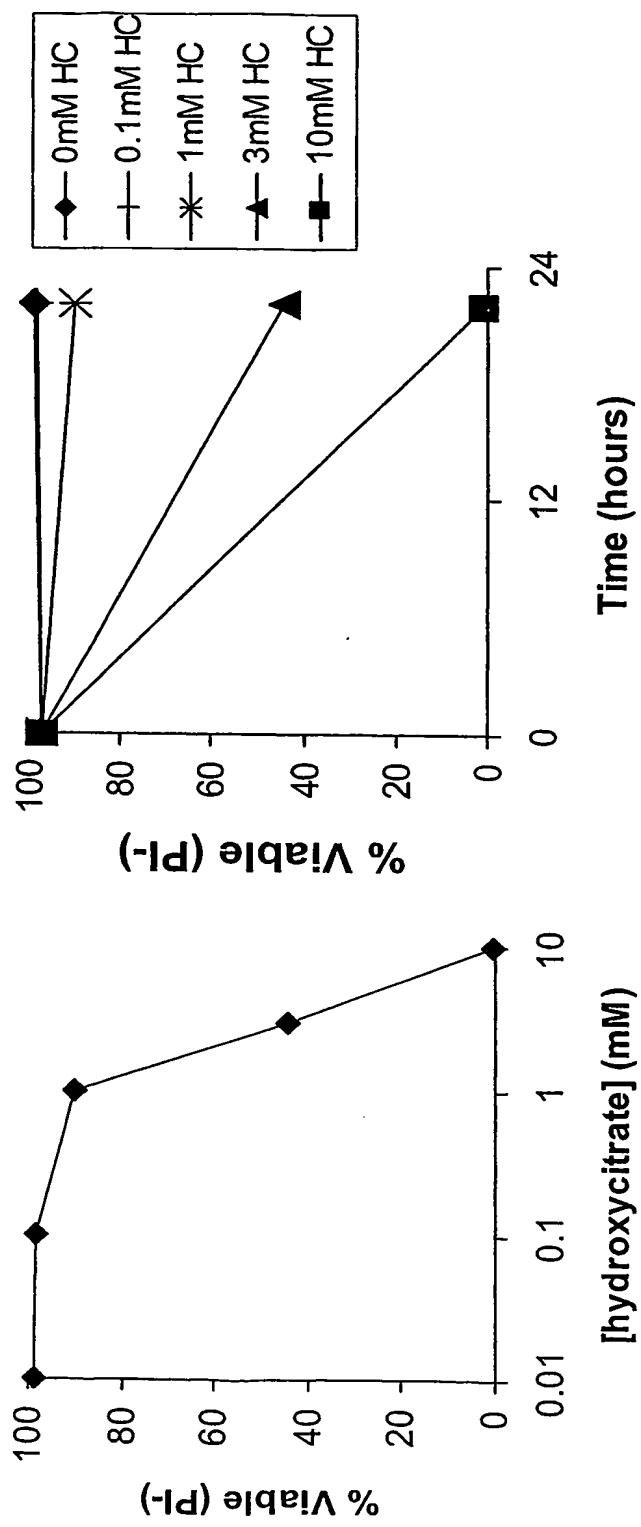
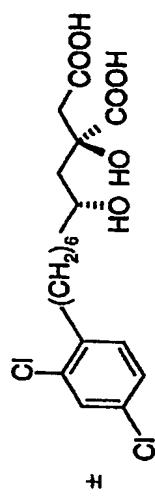


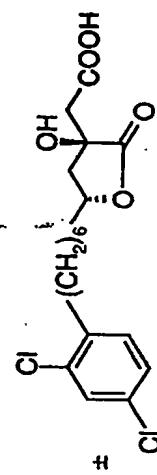
Figure 3

# Structure of a potent ACL inhibitor and its prodrug

SB-201076



SB-204990



**Figure 1** Structure of SB-201076 and its  $\gamma$ -lactone SB-204990

Figure 4

Pierce N.J., et al. (1998) The role of ATP citrate-lyase in the metabolic regulation of plasma lipids. Biochem J. 334, p113-119

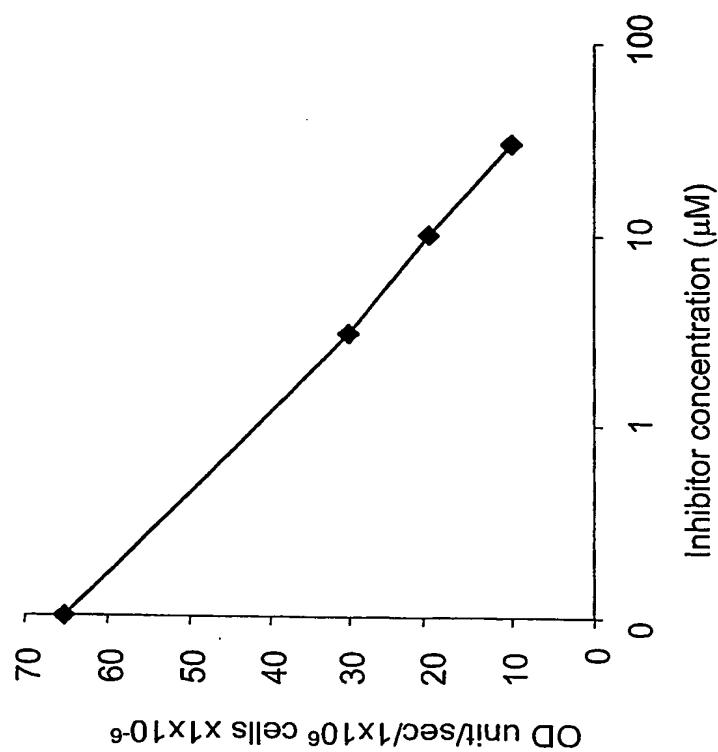
**SB201076 inhibits ACL activity in a dose-dependent fashion**

Figure 5

**SB204990 inhibits cell proliferation and survival  
in a dose-dependent fashion at micromolar concentrations**

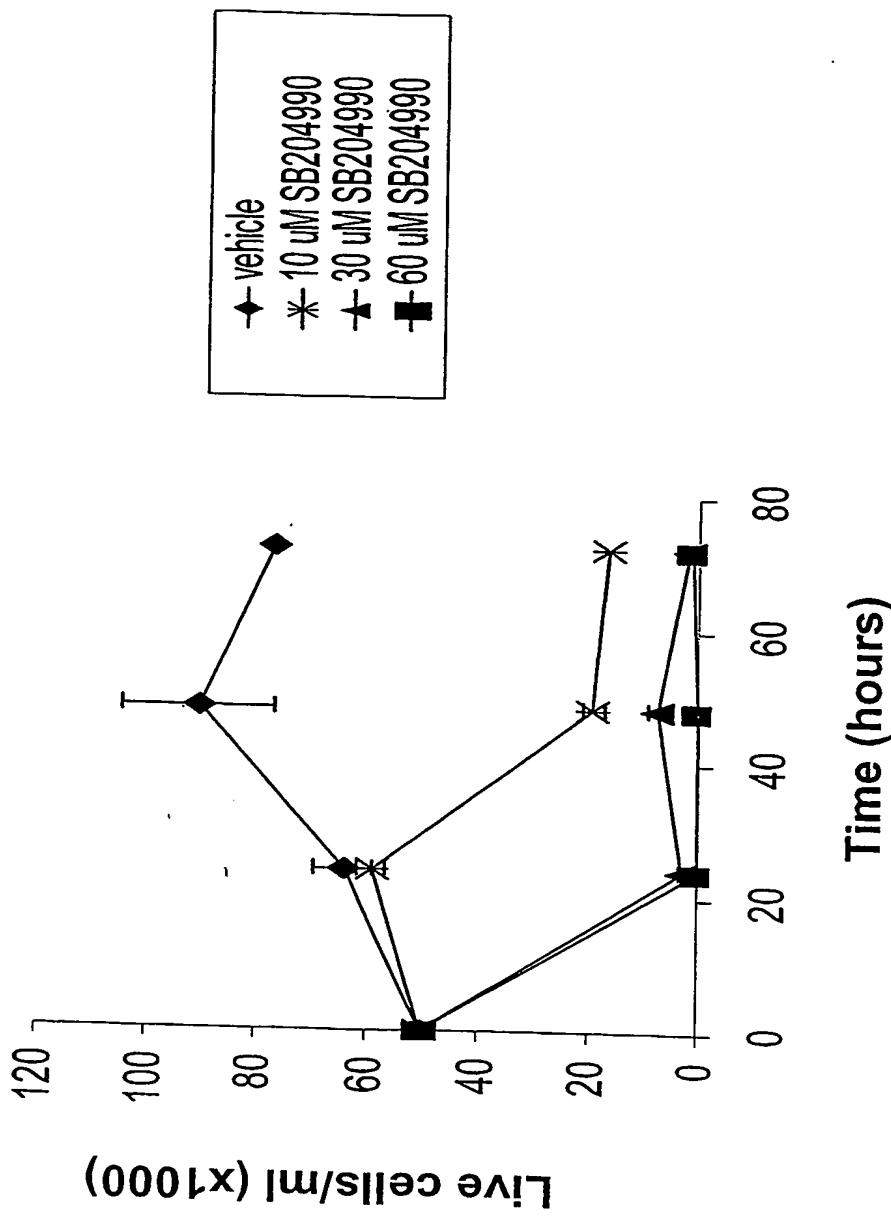
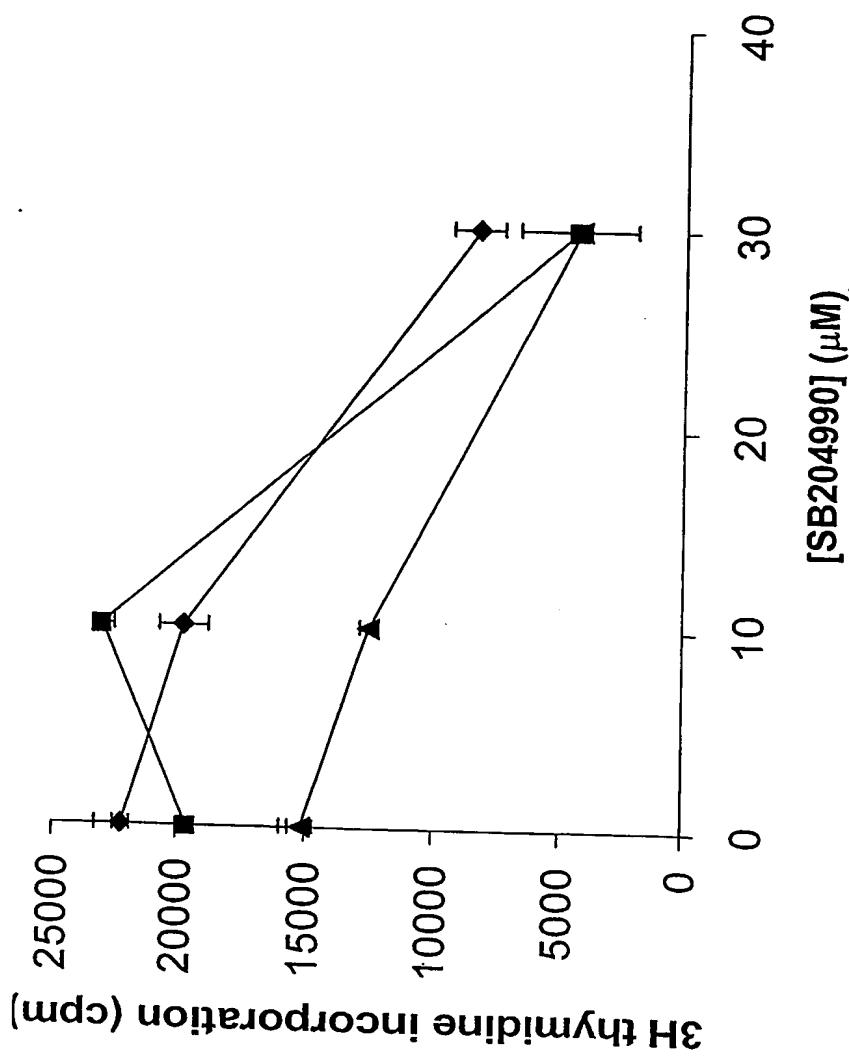


Figure 6

**ACL inhibition prevents the proliferation of immortalized hematopoietic cells in a dose-dependent fashion**



(3 independent FL5.12 stable clones treated with the drug in the presence of IL3 for 20 hrs)

Figure 7

## ACL inhibition causes G1 arrest and apoptosis of proliferating cells

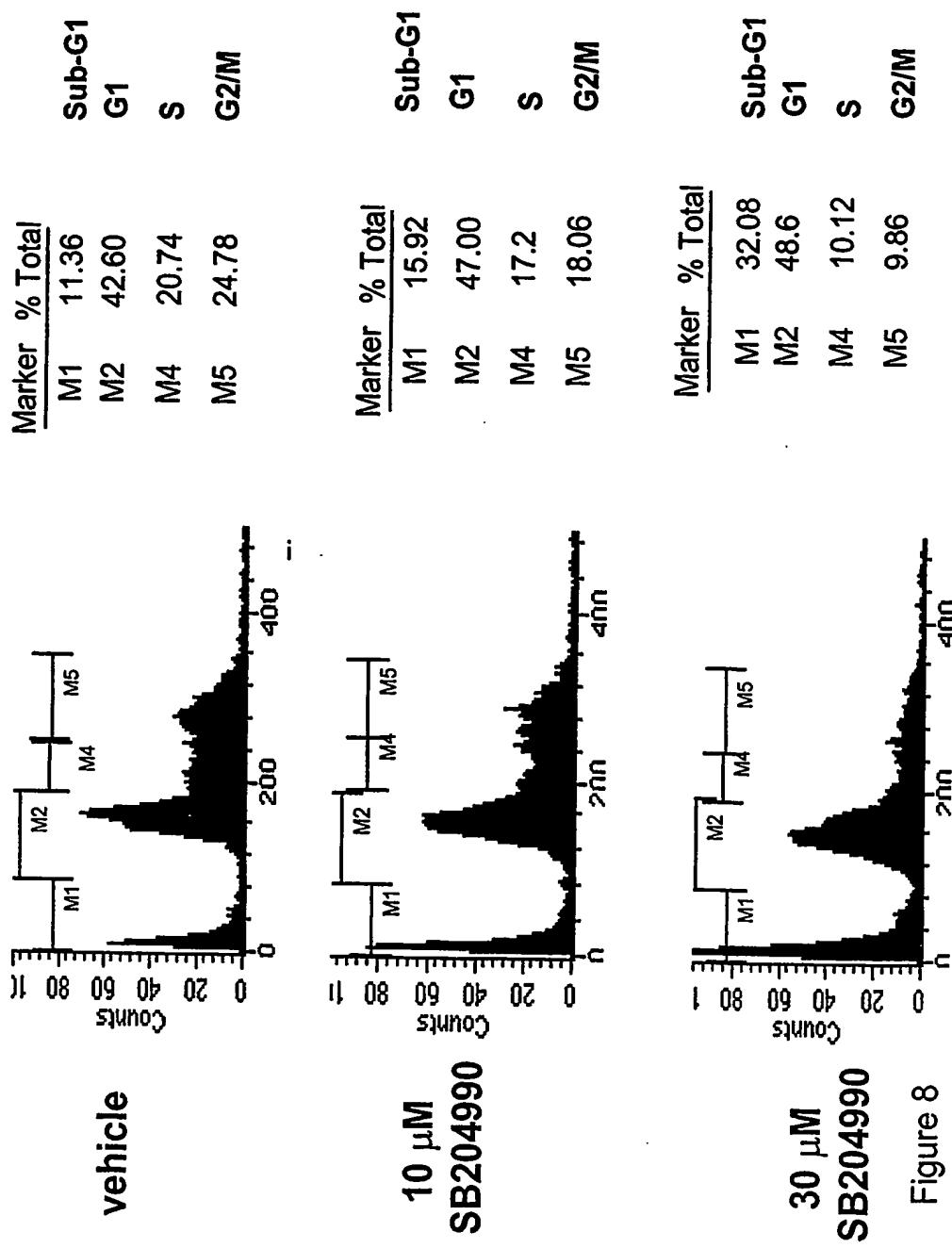


Figure 8

## ACL inhibition induces the surface expression of the apoptotic marker Annexin V in a dose-dependent fashion

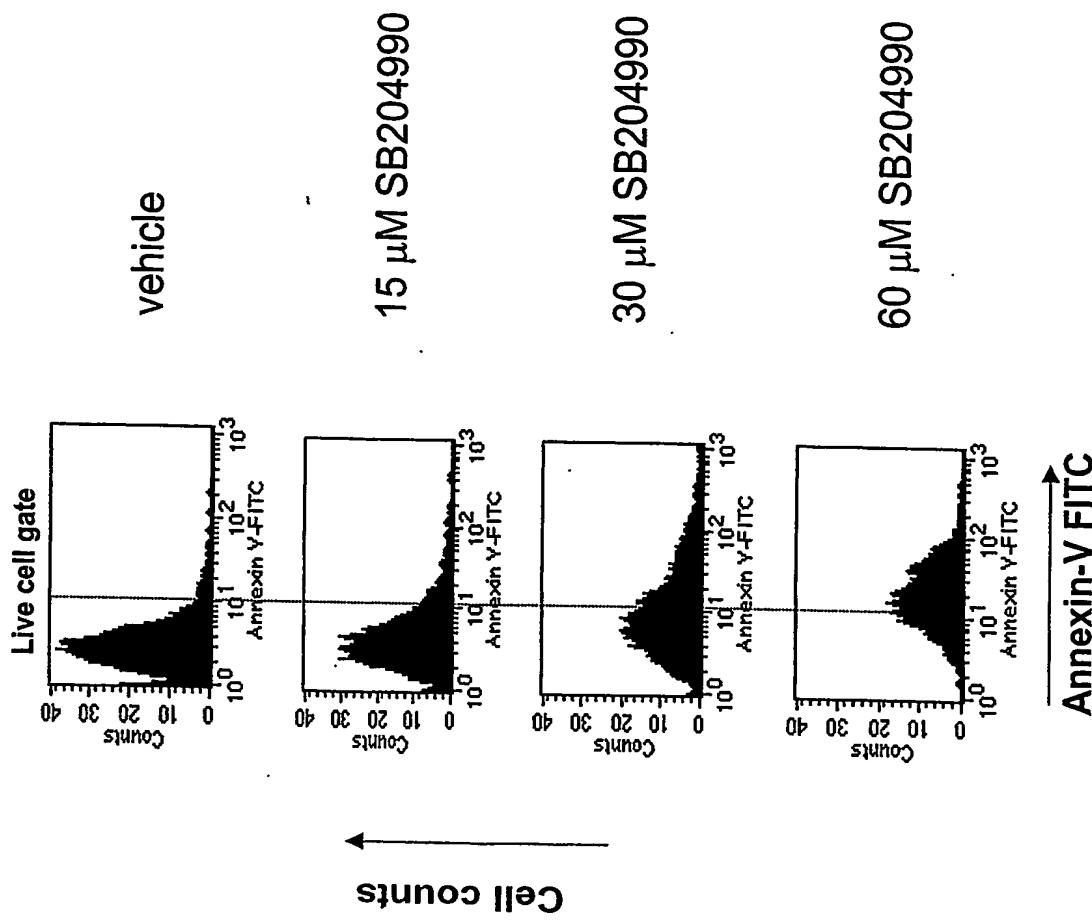


Figure 9

## Akt induces ACL activity independently of growth factor availability

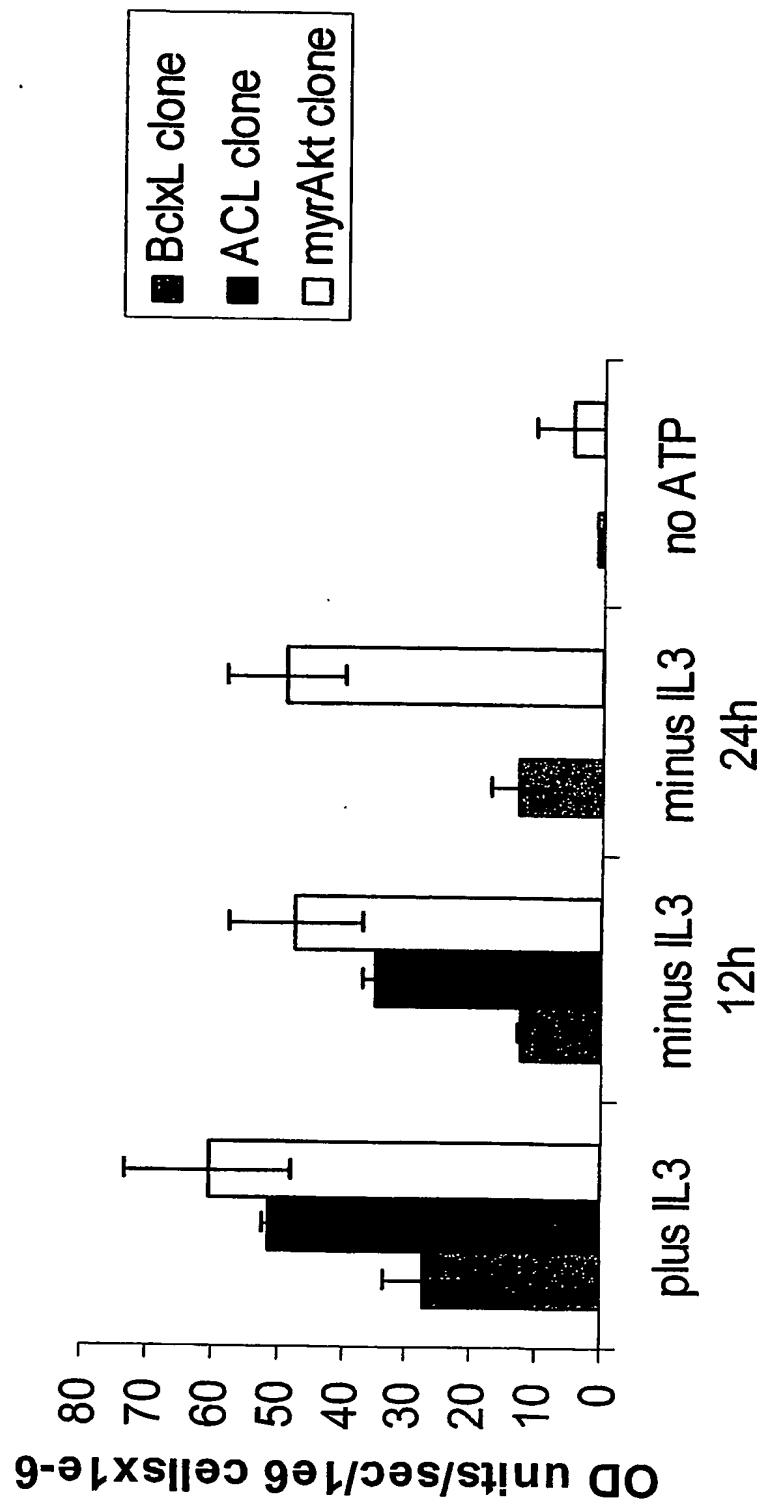


Figure 10

**ACL inhibition is selectively toxic to proliferating cells  
and to cells expressing active Akt**

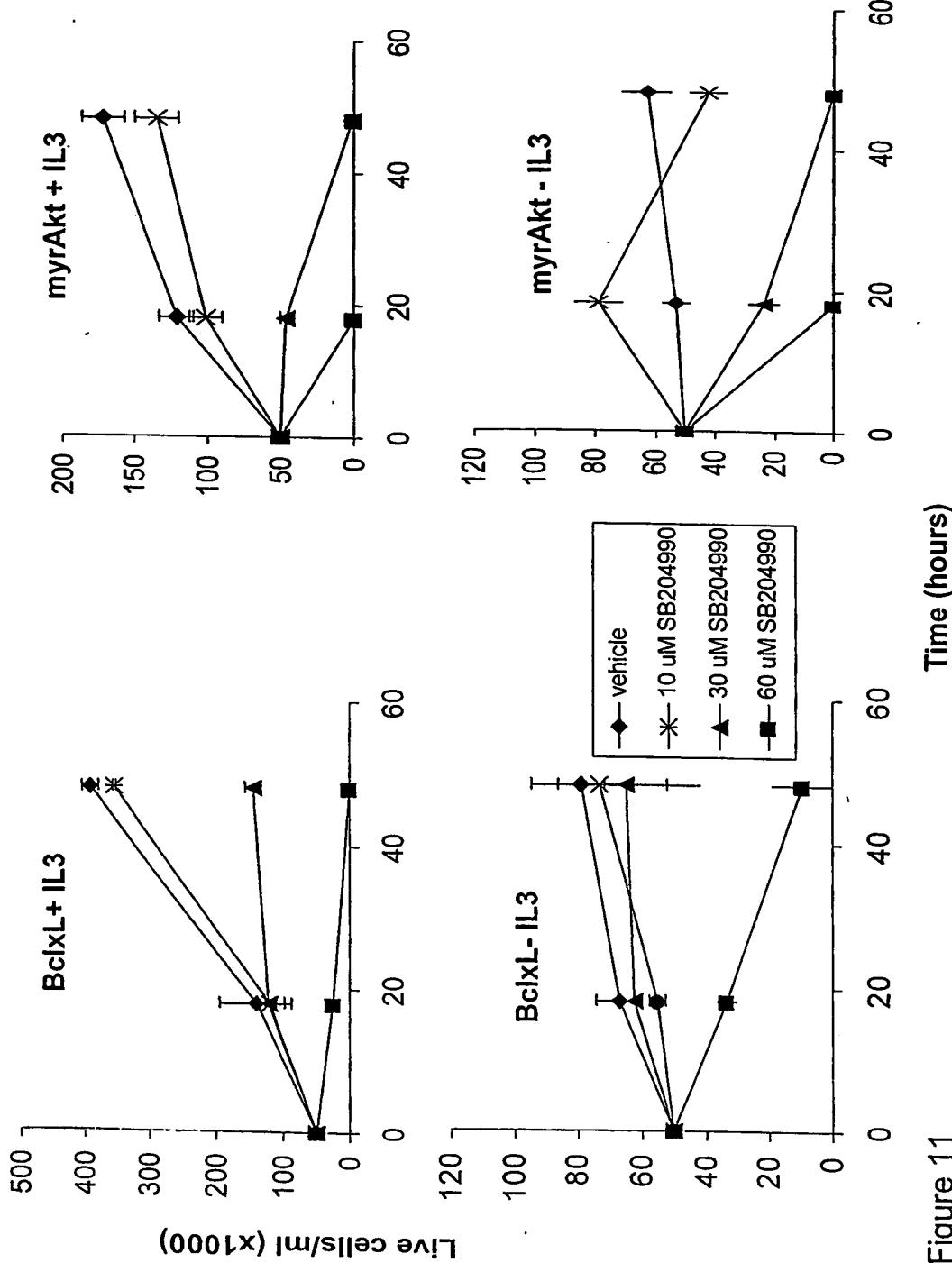


Figure 11

**Glioblastoma cell lines' response to ACL inhibition correlates with their activated Akt status**

A

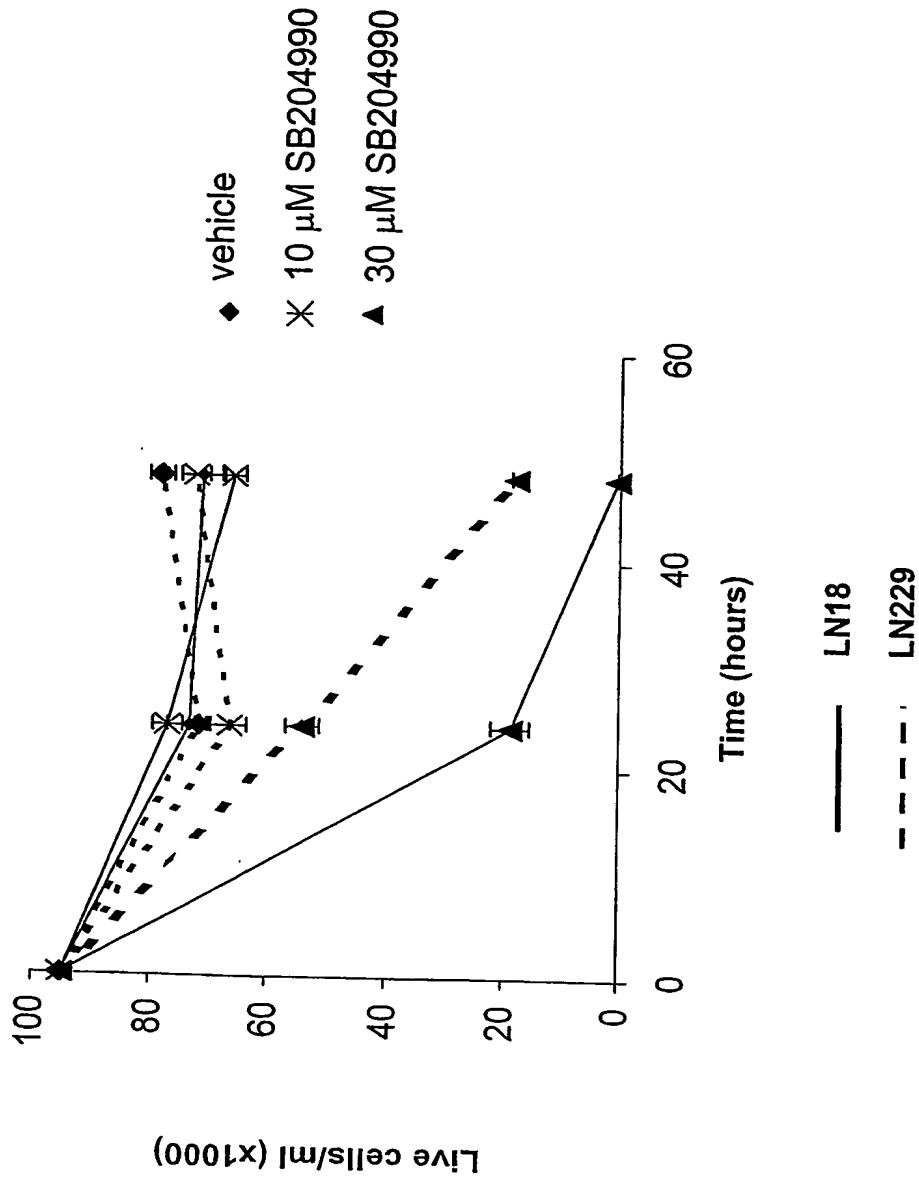


Figure 12A

## Glioblastoma cell lines' response to ACL inhibition correlates with their activated Akt status

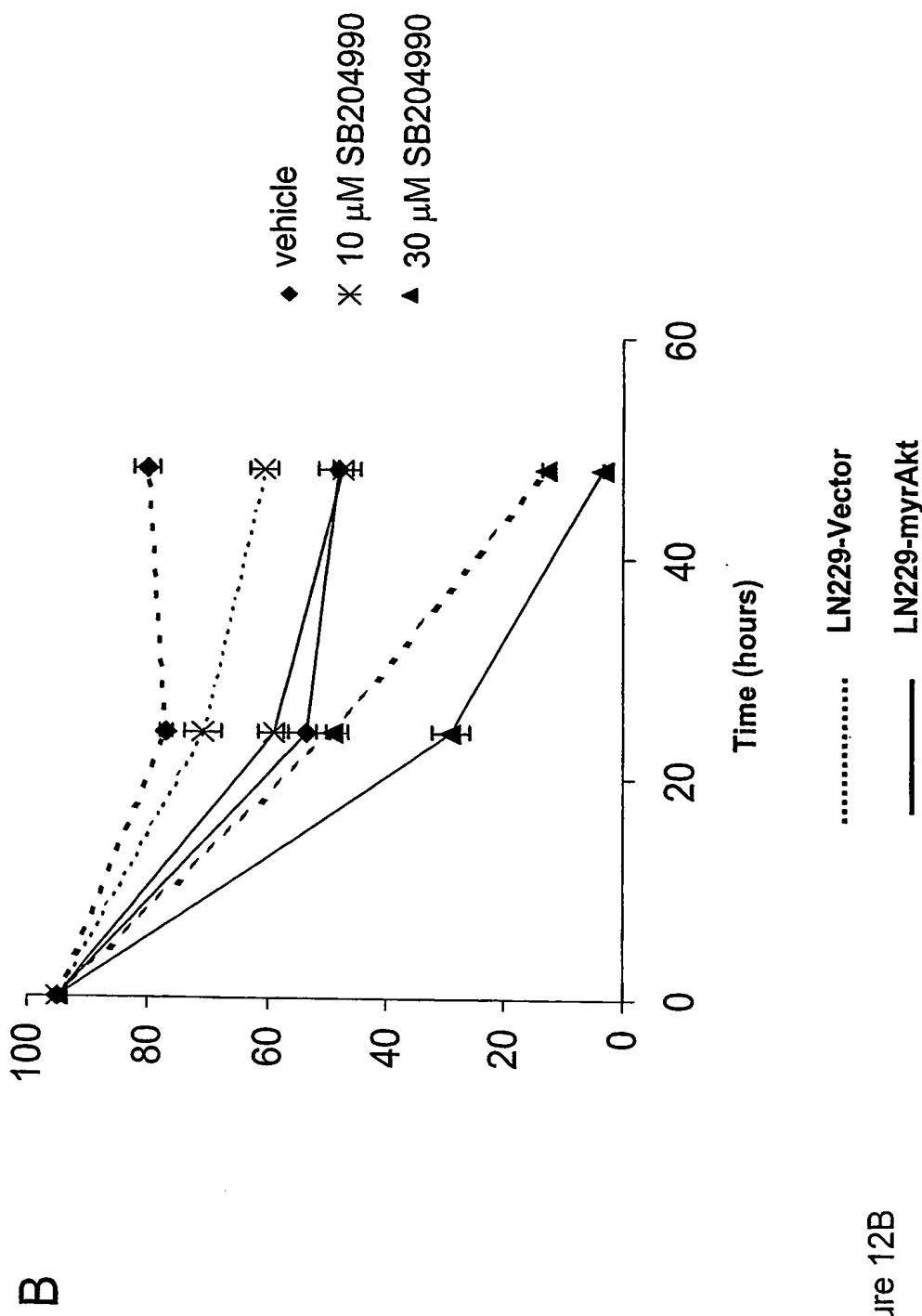


Figure 12B

**Proliferating cells are more sensitive to  
ACL inhibition-induced apoptosis**

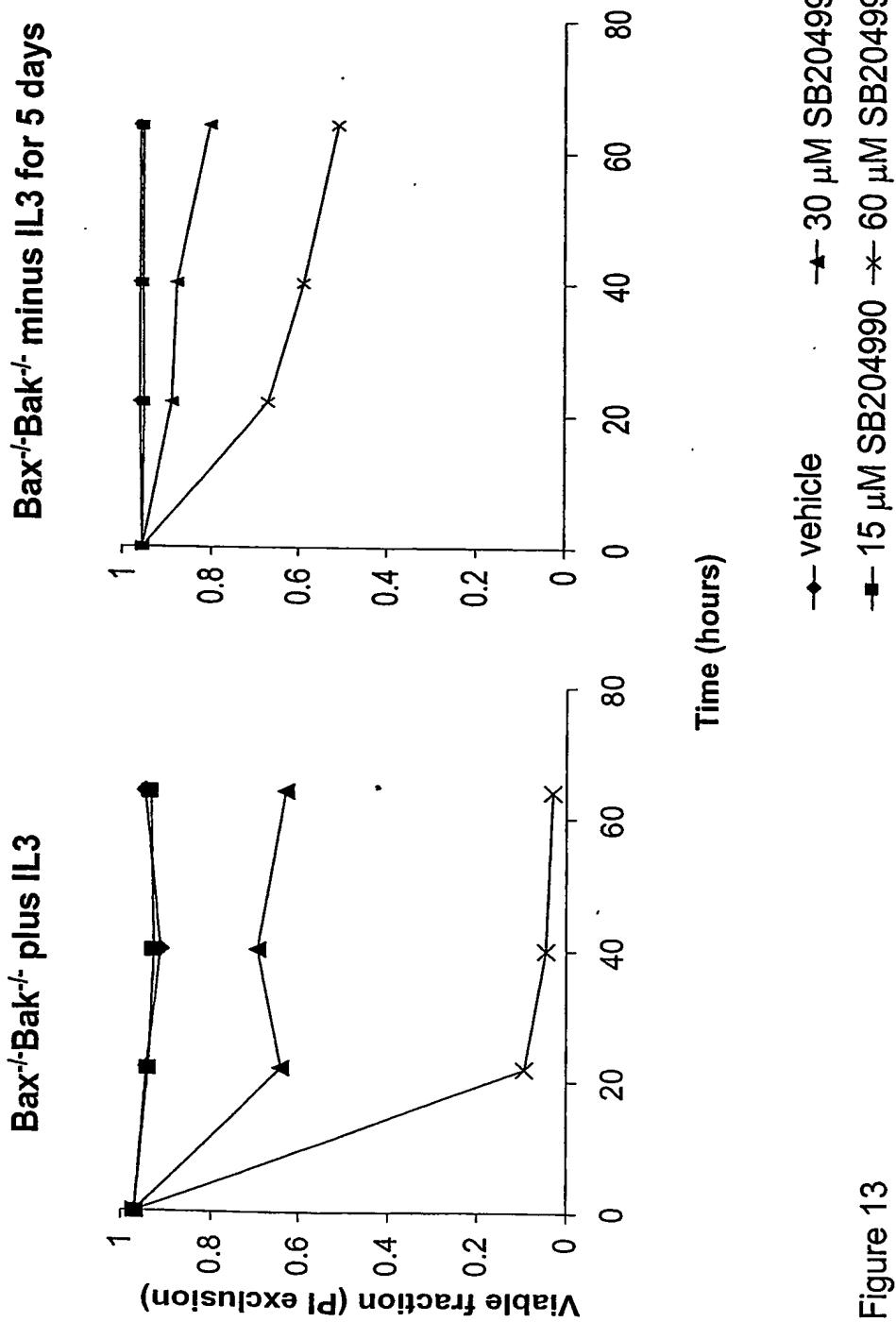


Figure 13

## ACL inhibition prevents growth factor-induced cell growth and cell cycle entry

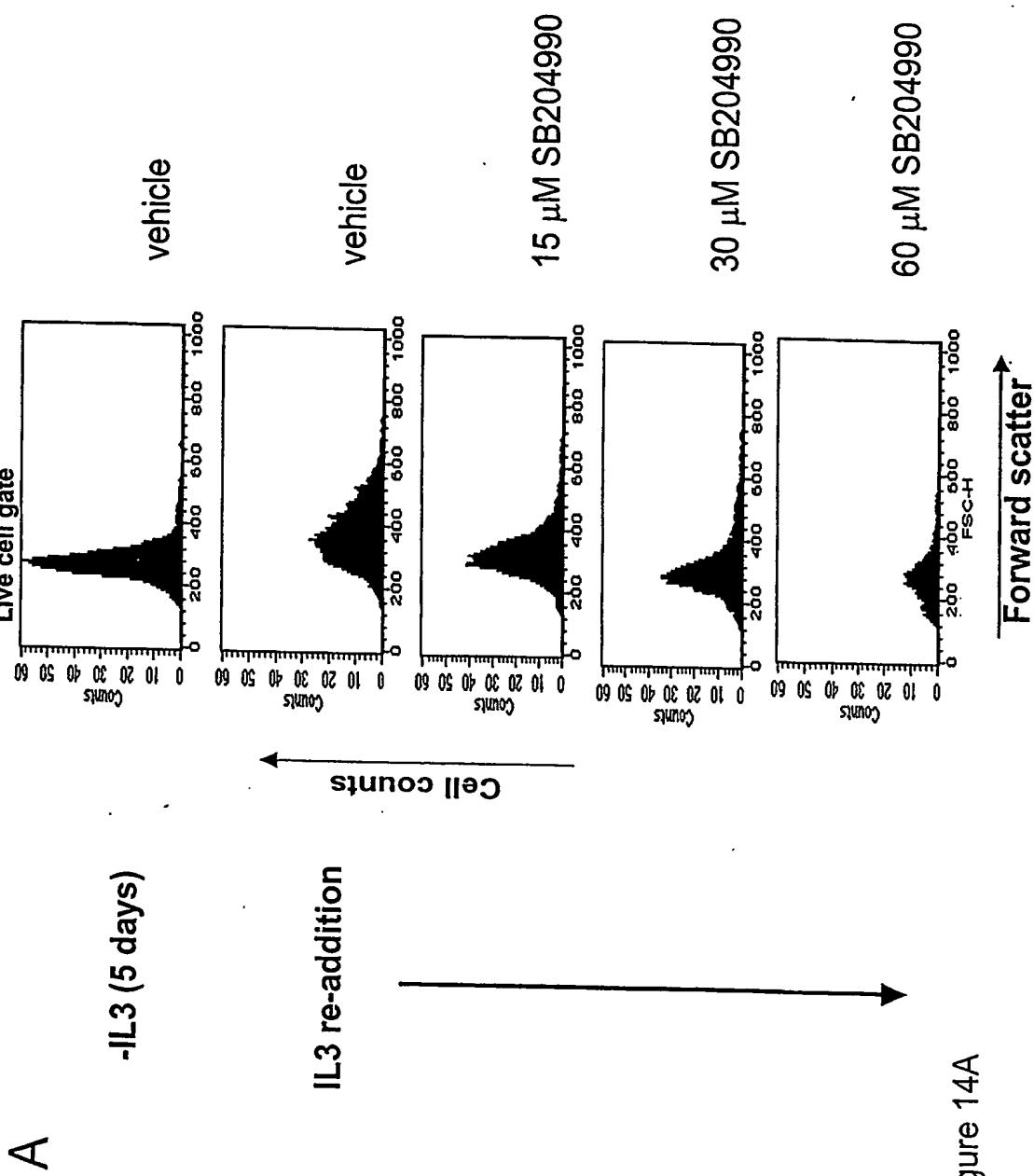


Figure 14A

## ACL inhibition prevents growth factor-induced cell growth and cell cycle entry

B

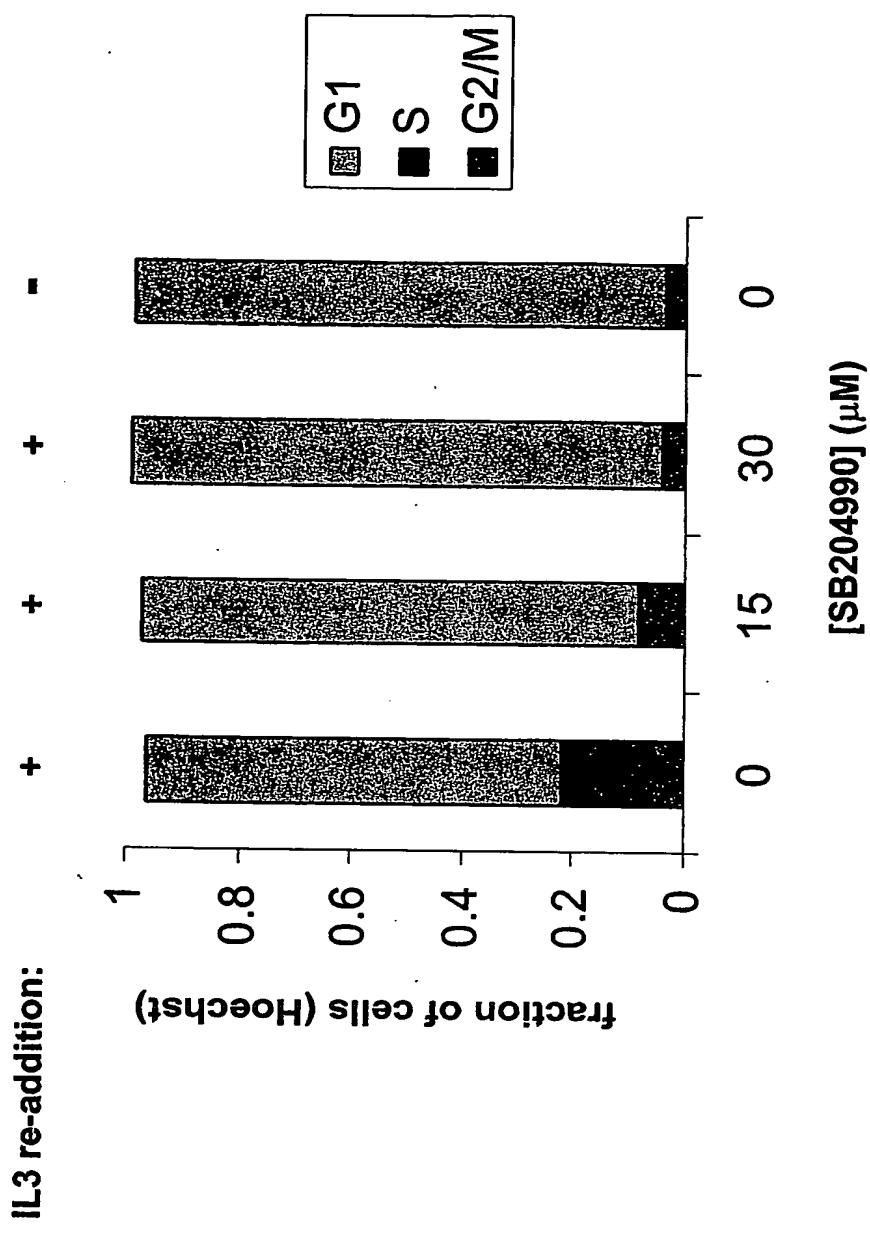


Figure 14B

**Mitogenic stimulation makes quiescent cells  
more sensitive to AICL inhibition-induced death**

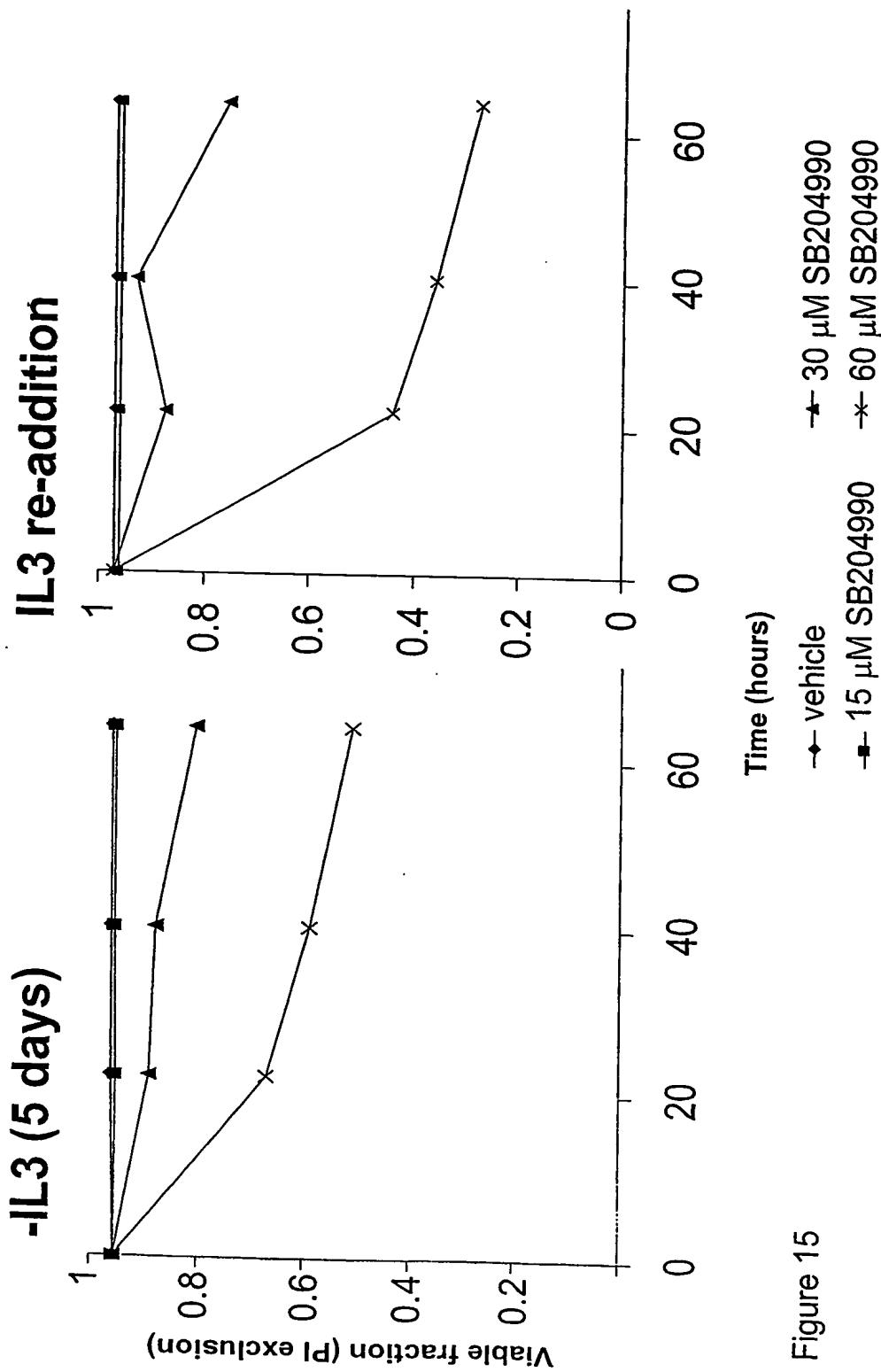


Figure 15

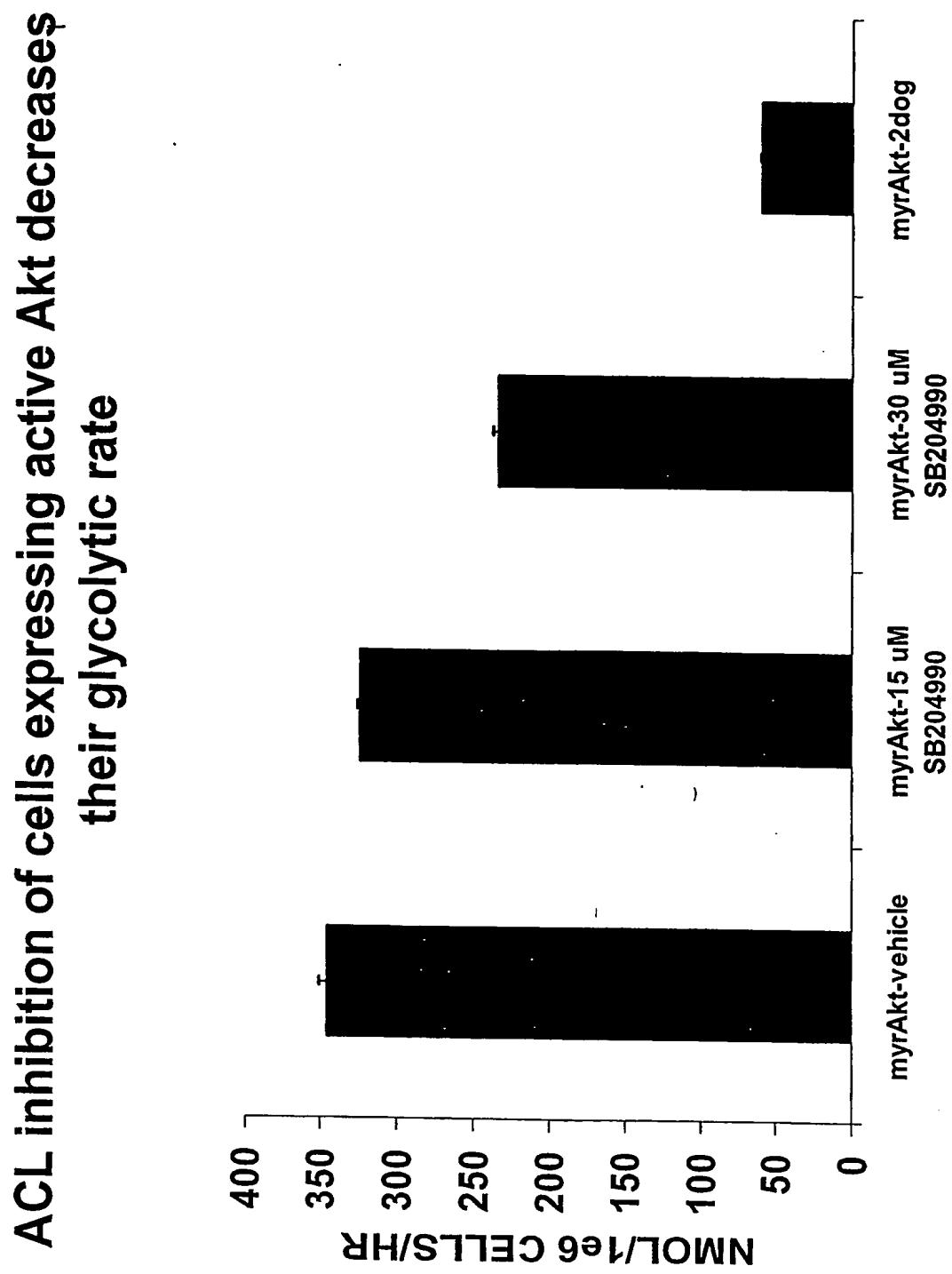


Figure 16

## Mitochondrial hyperpolarization upon AChL inhibition is dose-dependent

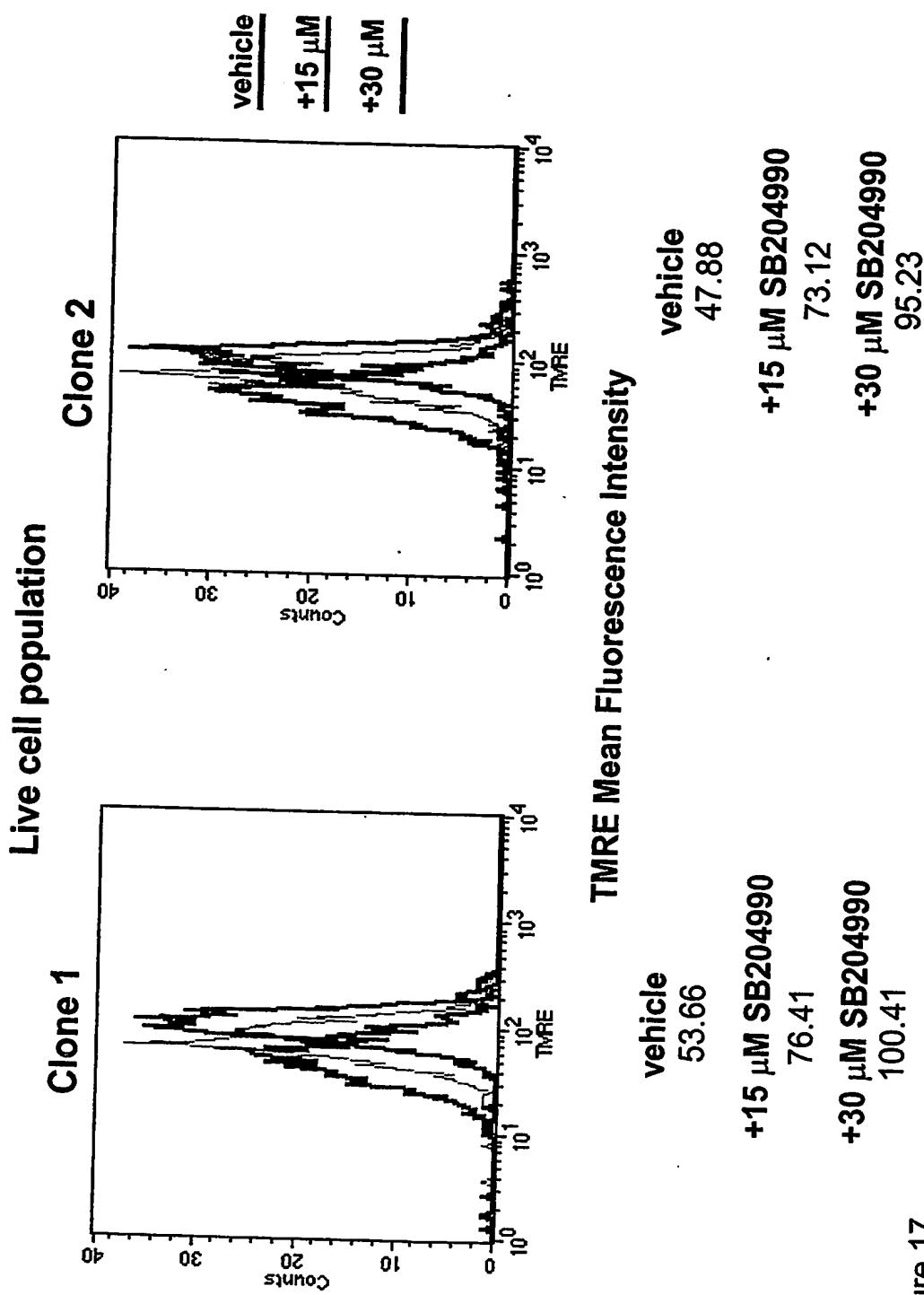


Figure 17

**ACL inhibition induced mitochondrial hyperpolarization  
precedes annexin V positivity**

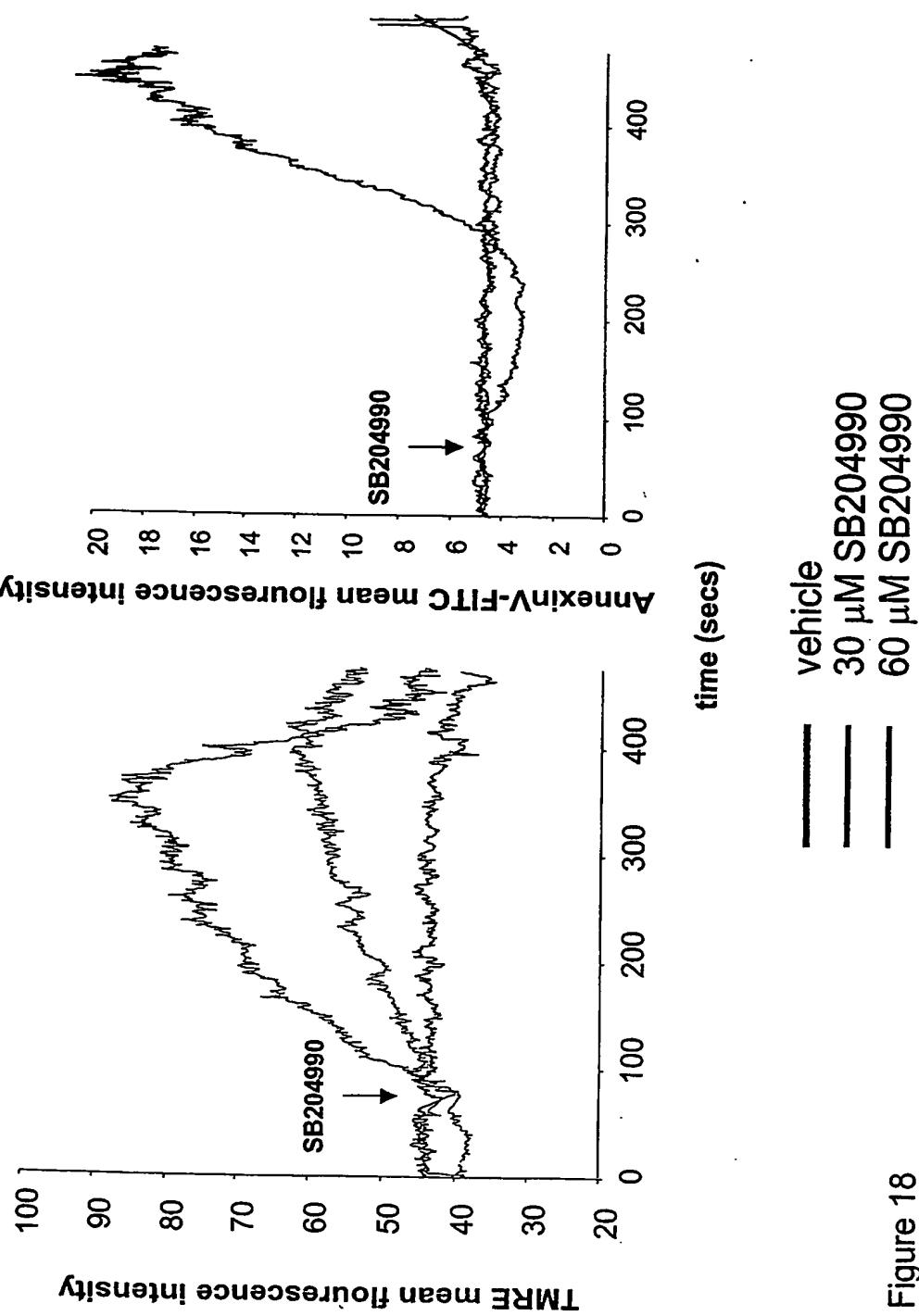


Figure 18